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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/667,283 | 09/17/2003 | Thomas A. Dobbins | 632898-041 | 8633 |

27805 7590 06/15/2006

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| EXAMINER | |
|---|---|
| GRAFFEO, MICHEL | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/667,283 | DOBBINS ET AL. | |
| | Examiner | Art Unit | |
| | Michel Graffeo | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 April 06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *7-11,21-25 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-20,26-33 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5 May 06 (1 sheet) 26 Nov 04 (1 sheet) 17 June 04 (4 sheets)
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group I in the reply filed on 10 April 2006 is acknowledged. The traversal is on the ground(s) that a serious burden will not be placed on the Examiner absent the Restriction. This is not found persuasive because the argument is an allegation without factual support that does not negate the basis for the restriction requirement as specifically set forth in the previous restriction requirement. In other words, the allegation that no serious burden is placed on the examiner does not negate the basis for the restriction.

Claims 7-11, 21-25 and 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

### *Status of Action*

Claims 1-6, 12-20, 26-33 and 37-39 are examined.

### *Claim Rejections - 35 USC § 112-2nd Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 12-20 and 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 15 contain the word safe, what is meant by safe, or rather what is safe versus effective. Claims 2-6, 12-14, 16-20 and 26-28 depend from claims 1 or 15.

### *Claim Rejections - 35 USC § 112-1st Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the Specification, while teaching the administration of the claimed composition for the purpose of elevating calcium levels and treating conditions related to calcium deficiencies, does not reasonably provide enablement for preventing hypocalcemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art.

In the instant case, applicants are claiming in part, a method of preventing a condition associated with calcium deficiency, specifically hypocalcemia, in a human by administering a pharmaceutical formulation containing a therapeutically effective amount of the compound calcium 3-hydroxy-3-methylbutyrate.

1) Nature of the invention.

The nature of the invention is directed to methods of preventing a condition in a human associated with the pathological effects of calcium deficiency, comprising administering the instant compound to a patient (human) in need thereof.

2) State of the prior art and the predictability or lack thereof in the art.

the ability of preventing hypocalcemia is not yet known in the art. The burden of enabling one skilled in the art to prevent hypocalcemia would be much greater than that of enabling the treatment of such diseases. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing hypocalcemia. Nor is there any guidance provided as to a specific protocol to

be utilized in order to show the efficacy of the presently claimed active ingredients for preventing hypocalcemia.

No experimental evidence supporting the contention that the claim specified actives would actually prevent this diseases by simply administering the claim specified active agents has been demonstrated nor practiced with the invention without an envisaged endpoint or result of the treatment (note the absence of such recitation in the current claim(s)). The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing and for practicing same without a specific endpoint for the treatment of the claimed diseases.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

the quantity of experimentation necessary; the quantity of experimentation would be undue to one of skill in the art and amount to the trial and error type of experimentation without a priori expectation of success. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing a condition associated with calcium and/or magnesium deficiency, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

4) Level of predictability in the art.

The art pertaining to the treatment of hypocalcemia remains highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art. Accordingly, treatments for conditions associated with calcium are normally tailored to the particular type of of mediator present, as there is none, and there can be no "magic bullet" for the prevention of hypocalcemia.

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is nowhere found in the specification. In particular, no working examples are provided. In addition, there is no apparent guidance as to what to expect or how to extrapolate preventing hypocalcemia, for example, from the data in the Specification.

6) Existence of working examples.

As discussed above, no working example is found.

7) Breadth of claims.

The breadth of the claims is directed to methods of preventing hypocalcemia comprising administering the instant compound to a patient (human) in need thereof.

8) Level of ordinary skill in the art.

In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing hypocalcemia, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 15-17 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Nissen US 4992470.

Nissen teach the parenteral (col 4 line 18) administration of a calcium salt (or edible butyrate salt thereof; col 2 lines 15-30) as well as additional alkaline earth metal salts, of which magnesium is one (claim 26) of HMB wherein the amount of Ca-HMB administered can be administered in an amount of 0.05 to .2 mgs/kg of body weight and up to an amount of 100 mg/kg of body weight per 24 hours (in current claims 4-6, 19-20 and 32-33; see col 3 lines 40-50 and col 4 lines 37-50) or in a human dose levels can range from 200 to 3,000 mgs per 24 hours (in current claims 4-6, 19-20 and 32-33; see col 4 lines 37-40). As noted on page 9 of the instant Specification, the active agent is highly soluble and therefore the administration of same under the same conditions and

same dosages as claimed will necessarily result in the same treatment i.e. the treatment of hypocalcemia.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 12-20, 26-33 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nissen US Patent No. 4992470 in view of Nissen US Patent No. 6031000.

Nissen ('470) teach the parenteral (col 4 line 18) administration (claims 1-6, 12-20 and 26-33) of a calcium salt (or edible butyrate salt thereof; col 2 lines 15-30) of HMB wherein the amount of Ca-HMB, or alkaline earth metals (in current claims 13-14;

see col 2 lines 35-40), administered can be administered in an amount of 0.05 to .2 mgs/kg of body weight and up to an amount of 100 mg/kg of body weight per 24 hours (in current claims 4-6, 19-20 and 32-33; see col 3 lines 40-50 and col 4 lines 37-50) or in a human dose levels can range from 200 to 3,000 mgs per 24 hours (in current claims 4-6, 19-20 and 32-33; see col 4 lines 37-40). The teachings in col 4 lines 30-50, reproduced below, encourage one of ordinary skill in the art to modify and optimize the dosage amounts in a 24 hour period (in current claims 4-6 and 19-20) to meet the limitations of claims 4-6 and 19-20:

> Purified HMB, either in free acid or in the form of an edible salt, can be used as a human immunostimulator. Either oral or parenteral administration can be used. For example, HMB may be administered orally in the form of tablets or capsules, or it may be administered dissolved in an intravenous parenteral solution. For parenteral administration, the sodium salt of HMB (Na-HMB) is preferred.
>
> Dose levels for a human subject can range from 200 to 3,000 milligrams (mg) per 24 hours. This administration can be repeated on a daily basis until the desired effect on the immune system is obtained. A preferred administration range is from 500 to 2,500 mg/24 hrs. Based on the presently available experimental information from animals models, it is believed that an optimum human dosage is from about 1 to 2 grams (gms) per day per 24 hrs. The dose level should be adequate so as to enhance the blastogenesis function of T lymphocytes. This is a function which can be monitored, and the dose required for the particular human subject can be regulated to obtain and maintain enhanced blastogenesis.

Moreover, the amounts provided allow for ratios of calcium and magnesium salts (alkaline earth metals) which fall into the 20:1 ratio (see for example, amounts of 100:5mgs – claims 13-14). As noted on page 9 of the instant Specification, the active

agent is highly soluble and therefore the administration of same under the same conditions and same dosages as claimed will necessarily result in the same treatment i.e. the treatment of hypocalcemia.

Nissen ('470) do not recite a composition with from 1 to 27% by weight of Ca-HMG or 13.7 mgs/ml for example, a composition comprising a ratio of Ca-HMG to Mg-HMG. Nonetheless, Nissen teach that other nontoxic salts can be used such as other alkali metal or alkaline earth metal salts (in current claims 3 and 18; see col 2 lines 35-40) and that the concentrations can be altered based on what is required and related to the total diet of the animal (see col 3 lines 35-40).

Nissen ('000) teach formulations such as a pharmaceutically acceptable forms which include, but are not limited to, solids, such as tablets or capsules, and liquids, such as intravenous solutions. Also, the composition can be administered utilizing any pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and examples of such carriers include various starches and saline solutions (in current claims 29-33; see col 3 lines 54-61). The '000 reference also teaches the use of the magnesium salt of HMG (see col 2 line 65). The composition used in the '000 reference preferably comprises from about 0.5 g to about 50 g of L-arginine, from about 0.5 g to about 50 g of L-glutamine, and from about 0.5 g to about 30 g of the calcium salt of HMB (in current claims 3 and 18; see col 4 lines 35-40).

One of ordinary skill in the art would have been motivated to combine the above references and as combined teach the claimed invention as claimed. One of ordinary skill in the art would have been motivated to combine the two references because both

are directed to the administration of a composition comprising Ca-HMG. Moreover, the "000 reference sites the "470 reference. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 12-20, 26-33 and 37-39 are provisionally rejected on the ground of obvious nonstatutory double patenting over claims 1-6 and 9-25 of copending Application No. 10/658075 in view of Nissen US Patent No. 6031000.. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully claimed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of treating a condition associated with calcium deficiency comprising administering Ca-HMG to a patient. Although the '075 reference claims the oral administration of Ca-HMG, one of ordinary skill in the art would have found oral administration obvious over parenteral administration and visa versa since the '000 reference for example teaches that the different administrable pharmaceutically acceptable forms include, but are not limited to, solids, such as tablets or capsules, and liquids, such as intravenous solutions.

Claims 1-6, 12-20, 26-33 and 37-39 are provisionally rejected on the ground of obvious nonstatutory double patenting over claims 1-6 and 9-24 of copending Application No. 10/797946. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully claimed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of treating a condition associated with calcium deficiency comprising administering Ca-HMG to a patient. Although the '075 reference claims the oral administration of Ca-HMG, one of ordinary skill in the art would have found oral administration obvious over parenteral

administration and visa versa since the '000 reference for example teaches that the different administrable pharmaceutically acceptable forms include, but are not limited to, solids, such as tablets or capsules, and liquids, such as intravenous solutions.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30 May 2006
MG

Ardin H. Marschel 6/11/06
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SUPERVISORY PATENT EXAMINER